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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/575,232	WITTE ET AL.	
	Examiner	Art Unit	
	QUANG NGUYEN, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12,14 and 17-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,14 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 1/10/09 was entered.

Amended claims 1-12, 14 and new claims 17-20 are pending in the present application, and they are examined on the merits herein.

Response to amendment

In light of Applicant's arguments, all of the prior art rejections set forth in the Office action mailed on 9/24/08 were withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 14 and 17-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the generation of chondrons comprising the step of **cultivation of chondrocytes** at unphysiologically high extracellular concentrations of magnesium (Mg), characterized in that at least once an unphysiologically high extracellular Mg concentration is increased during the cultivation, and **wherein said high extracellular concentrations of Mg range up to 20 mM**;

does not reasonably provide enablement for **a method for the generation of chondrons using any other cells and/or at any other unphysiologically high**

extracellular concentrations of Mg as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

This is a new ground of rejection.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The instant specification is not enabled for a method for the generation of chondrons as broadly claimed for the following reasons.

1. The breadth of the claims

The claims are directed to a method for the generation of chondrons comprising the step of cultivation of **any cells**, not necessarily limited to differentiated chondrocytes or chondrodrocyte precursors and including any differentiated cells such as hepatocytes, fibroblasts, neurons, **in both *in vitro* and *in vivo* at any unphysiologically high extracellular concentrations of a magnesium,** including any unphysiolocially high extracellular concentrations of Mg in excess of 0.9 mM (e.g., 10 mM, 20 mM, 50 mM, 100 mM, 250 mM, 500 mM), and **characterized in that at least once an unphysiologically high extracellular Mg concentration is increased to**

another unphysiologically high extracellular concentration of Mg during cell cultivation.

2. The state of the prior art and the unpredictability of the prior art

At the effective filing date of the present application (10/10/03), little was known on the effect of unphysiological high extracellular concentration of magnesium on cells other than chondrocytes cultured *in vitro* as evidenced at least by the teachings of Egerbacher et al. (Vet Pathol 38:143-148, 2001; Cited previously), Valletta, G. (US 6,248,368; IDS), Garcia et al. (US 6,211,143; IDS) and Halvorsen et al. (US 6,841,150; Cited previously). Egerbacher et al disclosed that magnesium supplementation at 1X concentration (0.0612 mg/ml MgCl + 0.0488 mg/ml MgSO4 = 1mM MgCl + 0.4 mM MgSO4) or **at 3X concentration (about 4.2 mM Mg)** has a significantly positive effect on quinoline-treated horse and dog chondrocytes in 5-day cultures containing 10% FCS; and the positive effects of Mg supplementation include decreased cell loss and morphologic changes (outspread, stellate chondrocytes vs more spindle-shaped or spherical cells of quinolone-treated and Mg-free chondrocytes) and a slightly increased cell proliferation (53% for Mg1 and 55% for Mg3) with respect to cells cultivated in Mg2+-free medium (47%; see page 146, col. 1, second paragraph; Figure 6). Valletta also disclosed a method for treating autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus and others, by administering orally **(dosage ranging 2 to 12 mg of magnesium per kg of body weight)** or parenterally (**dosage ranging from 2 to 30 mg/kg body weight daily)** a pharmaceutically acceptable composition suitable for releasing magnesium ions (e.g., organic or inorganic

magnesium salts or complexes thereof) to a patient in need thereof (see at least the abstract; col. 3, line 31 continues to line 11 of col. 6; col. 5, lines 12-57). Even assuming that the maximal daily parenteral dosage of 30 mg magnesium/kg body weight is all available in blood, this dosage is only equivalent to about 15 mM magnesium assuming the molecular weight of magnesium is 24.3 g, blood is about 0.08% of body weight and 1 kg of blood is 1L). However, Valletta et al disclosed explicitly that **when blood magnesium levels are over 4 mM, a total loss of tendon reflex occurred, followed by myoparalysis, hypothermic coma and cardiac arrest** (col. 6, lines 3-6). Garcia et al also taught a method for increasing cartilaginous mass of joints in a mammal by administering orally on a daily basis of a preparation comprising hydrolyzed gelatin and from 0.25 mg to 15 mg of magnesium per kilogram of body mass of the mammal (see at least the abstract)

3. The amount of direction or guidance provided

Apart from the exemplifications showing the effect of magnesium sulfate on cultured chondrocytes, cultured chondrocytes encapsulated in alginate beads and these treated chondrocytes, wherein the maximal concentration of magnesium sulfate tested was 20 mM (examples 1-3), the instant specification fails to provide sufficient guidance for a skilled artisan on how generate chondrons by cultivating cells other than chondrocytes and/or at unphysiologically high extracellular concentration of magnesium in excess of 20 mM in vitro, let alone in vivo. There is no evidence in the prior art nor in the instant specification that any differentiated cell as encompassed by the instant claims can be cultivated in either in vitro or in vivo to generate chondrons. Moreover,

even 3 years after the effective filing date of the present application (10/10/2003) Feyerabend et al (Tissue Engineering 12:3545-3556, 2006) still demonstrated that **unphysiologically high magnesium concentration supplementation has adverse effects on chondrogenesis by inhibiting extracellular matrix formation (see abstract and Figures 6-7), magnesium concentration at 20 mM already led to a significant inhibition of chondrocyte proliferation (Figure 1), and the highest magnesium concentration that was tested was 30 mM in a proliferation assay**. Furthermore, Valletta et al already disclosed that when blood magnesium levels are over 4 mM, a total loss of tendon reflex occurred, followed by myoparalysis, hypothermic coma and cardiac arrest (col. 6, lines 3-6). The instant specification fails to provide any evidence indicating that any unphysiological high magnesium concentration in excess of 20 mM would be beneficial for the growth and/or differentiation of cultured chondrocytes or chondrocytes precursors, let alone for any cells in the generation of chondrons in the methods as broadly claimed. Since the prior art at the effective filing date of the present application does not provide such guidance for the above mentioned issues, it is incumbent upon the present application to do so.

Furthermore, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues set forth above, the state of the relevant physiological art on the generation of chondrons at unphysiologically high extracellular concentrations of magnesium, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12, 14 and 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection.***

Independent claim 1 and its dependent claims recite the limitation "**the unphysiologically high extracellular Mg concentration**" in lines 2-3 of claim 1. There is insufficient antecedent basis for this limitation in the claim. Which particular high extracellular concentrations of magnesium concentrations do Applicants specifically refer to? Clarification is requested because the metes and bounds of the claims are not clearly determined.

Claims 6-7 and their dependent claims recite the limitation "chondrocytes" in line 1 of claims 6-7. There is insufficient antecedent basis for this limitation in the claim. This is because in independent claim 1 from which they are dependent on, there is no recitation of any chondrocytes. Clarification is requested because the metes and

bounds of the claims are not clearly determined. Additionally, in claims 11-12 and 19-20, it is also unclear what does the term "the cells" refer to? Does it refer to the cultivated cells in independent claim 1 or chondrocytes in either claim 6 or claim 7?

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 5 and 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Caruso (US 4,978,661) in view of Egerbacher et al. (Vet Pathol 38:143-148, 2001; Cited previously). ***This is a new ground of rejection.***

Within the scope of enablement, Caruso discloses a method of treating rheumatoid arthritis comprising administering to a patient, including intra-articularly

injecting, a therapeutically effective amount of 6-halo-4-quinolone derivatives (see at least the abstract and issued claims). Caruso also teaches that the "**multilocal" intra-articular treatment** with 6-halo-4-quinolone derivatives induce at least the clinical remission of the early rheumatoid illness (col. 3, lines 60-68; col. 4, lines 1-6). Caruso further discloses that 6-halo-4-quinolone derivatives are already known in the art and they are described as antimicrobial agents useful in the treatment of urinary and respiratory infections (col. 2, lines 22-31).

Caruso did not teach a method of culturing chondrocytes in the presence of an unphysiologically high extracellular concentration of magnesium, and wherein at least once the unphysicologically high extracellular Mg concentration is increased during the culture.

However, at the effective filing date of the present application Egerbacher et al already taught that **magnesium supplementation at 1X concentration (0.0612 mg/ml MgCl + 0.0488 mg/ml MgSO4 = 1mM MgCl + 0.4 mM MgSO4) or at 3X concentration (about 4.2 mM Mg) has a significantly positive or protective effect on quinoline-treated horse and dog chondrocytes in 5-day cultures, with more positive effects observed for a triple dose** (see at least the abstract; Figures 1-5; page 144, col. 1, second paragraph; and section titled "Magnesium supplementation"). Egerbacher et al further disclosed that the addition of Mg2+ slightly increased cell proliferation (53% for Mg1 and 55% for Mg3) with respect to cells cultivated in Mg2+-free medium (47%; see page 146, col. 1, second paragraph; Figure 6).

It would have been obvious for an ordinary skilled artisan to modify the teachings of Caruso by also intraarticularly injecting magnesium and maintaining magnesium (including repeated injections) at a concentration within a range of 1.4 mM to 4.2 mM for the arthritic joint of a patient treated with 6-halo-4-quinolone derivatives in light of the teachings of Egerbacher et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Egerbacher et al already showed at least protective effects of Mg supplementation at a concentration within a range of 1.4 mM and 4.2 mM for horse and dog chondrocytes against quinolones in tissue cultures, and that Mg2+ supplementation also slightly increased cell proliferation.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Caruso and Egerbacher et al.; coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1-2, 4-9, 14 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Masuda et al. (US 2001/0012965) in view of Egerbacher et al. (Vet Pathol 38:143-148, 2001; Cited previously), Halvorsen et al. (US 6,841,150), and Lindenberg et al (US 2005/0239040). ***This is a new ground of rejection.***

Within the scope of enablement, Masuda et al already disclose at least a method for producing a transplantatble cartilage matrix, comprising culturing isolated chondrogenic cells, including human adult articular chondrocytes, in alginate culture containing a stimulatory agent, such as fetal bovine serum and/or exogenously added specific growth factors such as osteogenic protein-1, TGF-beta, insulin like growth factor, for an amount of time effective for allowing formation of a chondrogenic cell-associated matrix (see at least Summary of the Invention; and particularly paragraphs 33-40 and example 1).

Masuda et al did not teach a method of culturing isolated chondrogenic cells in the presence of an unphysiologically high extracellular concentration of magnesium, wherein the unphysiologically high extracellular Mg concentration is increased at least once during the cell culture and/or the cultured chondrocytes are differentiated from adult stem cells.

However, at the effective filing date of the present application Egerbacher et al already taught that **magnesium supplementation at 1X concentration (0.0612 mg/ml MgCl + 0.0488 mg/ml MgSO4 = 1mM MgCl + 0.4 mM MgSO4) or at 3X concentration (about 4.2 mM Mg) has a significantly positive or protective effect on quinoline-treated horse and dog chondrocytes in 5-day cultures, with more positive effects observed for a triple dose** (see at least the abstract; Figures 1-5; page 144, col. 1, second paragraph; and section titled "Magnesium supplementation"). Egerbacher et al further disclosed that **the addition of Mg2+ slightly increased cell**

proliferation (53% for Mg1 and 55% for Mg3) with respect to cells cultivated in Mg2+-free medium (47%; see page 146, col. 1, second paragraph; Figure 6).

Additionally, Halvorsen also disclosed at least a method for directing adipose-derived stromal cells cultivated *in vitro*, including in a calcium alginate or another biocompatible lattice or matrix capable of supporting chondrogenesis in a three dimensional configuration, to differentiate into functional chondrocytes in conditions such as at temperatures between 31 ^{o}C to 37 ^{o}C in a humidified incubator, with a carbon dioxide content to be maintained between 2% to 10% and the oxygen content between 1% and 22% (see at least Summary of Invention; particularly col. 5, line 54 continues to line 7 of col. 6; col. 6, lines 61-65).

Moreover, at the effective filing date of the present application Lindenberg also taught an **in vittro culture method for obtaining a mature oocyte in which the oxygen tension, a cell culture parameter, is regulated via a temporal rise or a temporal decrease in oxygen tension in one or more times** (see at least the abstract and paragraphs 89-100,154-159).

It would have been obvious for an ordinary skilled artisan to modify the teachings of Masuda et al by also culturing and maintaining isolated chondrogenic cells (including a temporal rise in the extracellular Mg concentration in one or more times) in the presence of a high extracellular concentration of Mg ranging between 1.4 mM and 4 mM, in light of the teachings of Egerbacher et al, Halvorsen et al and Lindenberg as discussed above.

An ordinary skilled artisan would have been motivated to carry out the above modification because Egerbacher et al already showed at least protective effects of Mg supplementation at a concentration within a range of 1.4 mM and 4.2 mM for horse and dog chondrocytes against quinolones in tissue cultures, and that Mg2+ supplementation also slightly increased cell proliferation. Additionally, cultivation of adipose-derived stromal cells in a calcium alginate culture to differentiate into functional chondrocytes was also taught by Halvorsen et al. Furthermore, Lindenberg already taught at least a cell culture parameter such as the oxygen parameter can be regulated via a temporal rise or a temporal decrease in one or more times in a cell culture.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Masuda et al, Egerbacher et al, Halvorsen et al and Lindenberg; coupled with a high level of skill for an ordinary skilled artisan in the relevant art.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/QUANG NGUYEN/
Primary Examiner, Art Unit 1633